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NEPHROLOGY - REVIEW

Anticoagulation in renal replacement therapies: Why heparin should be abandoned in critical ill patients?

Pilar Musalem[1,2] · Cristian Pedreros-Rosales[1,2] · Hans Müller-Ortiz[1,2]

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Abstract

Extracorporeal circuits used in renal replacement therapy (RRT) can develop thrombosis, leading to downtimes and reduced therapy efficiency. To prevent this, anticoagulation is used, but the optimal anticoagulant has not yet been identified. Heparin is the most widely used anticoagulant in RRT, but it has limitations, such as unpredictable pharmacokinetics, nonspecific binding to plasma proteins and cells, and the possibility of suboptimal anticoagulation or bleeding complications, specifically in critically ill patients with acute renal failure who are already at high risk of bleeding. Citrate anticoagulation is a better alternative, being considered a standard for continuous renal replacement therapy, since it is associated with a lower risk of bleeding complications and better efficacy, even in patients with acute renal failure or liver disease. The aim of this article is to provide an updated review of the different strategies of anticoagulation in renal replacement therapies that can be implemented in critical scenarios, focusing on the advantages and disadvantages of each one and the beneficial aspects of using citrate over heparin in critical ill patients.

Keywords Renal replacement therapy · Anticoagulation · Heparin · Citrate · Extracorporeal Circuit

Introduction

Under physiological conditions, linear blood flow through healthy endothelium prevents activation of the coagulation cascade. However, in the extracorporeal hemodialysis circuit, there are different factors that influence the development of hemoconcentration, protein polarization and thrombotic phenomena, such as dialyzer biocompatibility, blood flow rate, and filtration fraction [1]. Clotting of the extracorporeal circuit impacts negatively on the therapy prescribed, representing a quarter of causes for stopping renal replacement therapies and consequently affecting patient-related outcomes [2].

After the interaction of the blood with the extracorporeal material occurs a progressive process of protein adsorption to the surface, with the consequent deposit of fibrinogen and other proteins such as coagulation factors, lipoproteins, albumin, and immunoglobulins [3, 4]. Factor XII is one of the main players involved, since it triggers thrombin synthesis and complement activation, generating a crosstalk between both systems and amplifying thrombin generation. The phenomenon of protein polarization also produces adherence of red blood cells, platelets, and inflammatory cells to the membrane, decreasing the efficiency of the dialysis membrane [5].

Additionally, critically ill patients and those with acute kidney injury may develop a prothrombotic state, secondary to the expression of tissue factor in endothelial and mononuclear cells, a decrease in natural anticoagulants, and inhibition of fibrinolysis [6], further contributing to decreased survival of the extracorporeal circuit.

In the previously mentioned factors lies the importance of the existence, implementation and reviewing the different methods existing to prevent thrombosis of extracorporeal circuits. This is essential, since circuit coagulation is the main cause of downtimes and stopping of renal replacement therapies, causing the patient to receive a lower dose of therapy in relation to the initially prescribed dose [2, 7, 8]. Multiple studies have been conducted to evaluate the effect

✉ Cristian Pedreros-Rosales
cpedreros@me.com

[1] Departamento de Medicina Interna, Facultad de Medicina, Universidad de Concepción, Concepción, Alto Horno 777, 4270918 Talcahuano, Región del Bío Bío, Chile

[2] Nephrology, Dialysis and Transplantation Service, Hospital Las Higueras, Alto Horno 777, 4270918 Talcahuano, Región del Bío Bío, Chile

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and safety of citrate versus heparin anticoagulation in critical patients receiving renal replacement therapies with the purpose of stablishing the best method to prolong the circuit life and though achieving the prescribed dose of therapy. Despite extensive literature of existing measures to prevent thrombosis of extracorporeal circuits, there remains a gap in our understanding of the most effective and safe anticoagulation strategies. This is fundamental in order to prescribe more targeted therapies and eventually optimize important patient outcomes like survival, length of stay, or medical complications (Table 1).

The objectives of this review are: (1) to describe and summarize the current strategies to prevent clotting of extracorporeal circuits, (2) to compare the advantages and disadvantages of heparin and citrate as anticoagulants in renal replacement therapies in critical ill patients, and (3) to discuss the potential benefits of citrate use in this scenario.

Measures to maintain the patency of the extracorporeal circuit

Strategies to achieve patency of the extracorporeal circuit are divided into non-pharmacological and pharmacological. Within the latter, there are systemic and regional protocols of anticoagulation [7].

Non-pharmacological

The presence of a properly functioning vascular access will prevent the development of out-of-range pressures, which generate a decrease in blood flow with the risk of coagulation of the circuit secondary to stasis and an increase in the filtration fraction. An adequate blood flow rate and ultrafiltration percentage will generate an optimal filtration fraction (< 25%) that will prevent hemoconcentration within the circuit. The priming of the circuit, which decreases the air–blood interface, and the rapid reaction to the appearance of alarms to avoid blood stasis are other important factors to apply [7, 9]. Although there is no high-quality evidence to support their use [10], they should be applied to all types of extracorporeal therapy, regardless of the type and use of anticoagulation.

Pharmacological

Anticoagulation reduces the risk of clotting in the circuit, increasing its survival and the effectiveness of renal replacement therapy. An optimal anticoagulant must deliver maximum anti-thrombotic activity with minimal risk of bleeding complications and negligible systemic effects. Additionally, it should be affordable, have a short half-life, and be simple to reverse. Furthermore, monitoring the anticoagulant effect must be straightforward and easily accessible. Although the ideal anticoagulant does not exist, the most widely used strategies in current clinical practice are systemic (heparins, thrombin antagonists, heparinoids, and platelet inhibitors) and regional (citrate and heparin–protamine) [11]. Both strategies include the use of heparin; however, several studies have shown superiority of regional citrate anticoagulation in terms of effective dose delivered, filter survival, and risk of major and minor bleeding [12–20], and continuous renal replacement therapy (CRRT) is currently the method of choice suggested by KDIGO [21]. Despite all this, the most widely used anticoagulant continues to be heparin [22].

How does heparin work and why should it be avoided in critical ill patients?

Unfractionated heparin (UFH) is a heterogeneous mixture of negatively charged sulfated glycosaminoglycans, which exert their anticoagulant action mainly through their interaction with antithrombin (AT), generating a conformational change in their structure, increasing, and accelerating their capacity to inactivate thrombin, activated factor X, and activated factor IX. The therapeutic goals for treatment with UFH are an aPTT of 45–60 s or anti-Xa activity levels 0.3–0.6 IU/mL (Fig. 1). Monitoring for LMWH is through anti-Xa activity (anti-Xa), with target levels of 0.25–0.35 IU/mL [11].

Since UFH is affordable and considered safe for repeated use, it is the most widely used anticoagulant in renal replacement therapies. It has a rapid onset of action (3–5 min) and short half-life (1 h) and is predominantly cleared by hepatic and vascular endothelial heparinases, but given their conformational characteristics, it binds non-specifically to other plasma proteins (platelet factor 4, fibronectin, and von Willebrand factor), as well as leukocytes, macrophages, and endothelial cells affecting its half-life and bioavailability, making it difficult to predict their effect, which is why they require close monitoring with aPTT [23, 24] (Fig. 2).

Low molecular weight heparin (LMWH) was implemented in general clinical practice given its better risk–benefit profile and pharmacokinetic properties (mainly longer half-life and better prediction of its therapeutic effect). It presents less binding to plasmatic and cellular proteins, less capacity to inactivate thrombin, but maintaining its capacity to inactivate factor X. Its monitoring is usually only necessary in clinical situations such as morbid obesity and renal failure, through anti-Xa levels, which are not widely available [25]. Regardless of this, LMWH was associated with a higher incidence of bleeding complications (11.4%) compared to UFH (2.3%) and citrate (2.0%) in CRRT (20), and there are insufficient data to support its use.

It is important to consider that in critical ill patients, there may be resistance to the action of heparin, secondary to the

Table 1 RCT comparing citrate versus heparin in continuous renal replacement therapies

Author	Therapies	Blood flow	Blood citrate concentration or iCa post-filter	Heparin dose or aPTT	Filter survival (hours)	Circuit clotting	Hemorrhage	Red blood cells transfusion	Metabolic alkalosis	Hypocalcemia
Monchi et al. [12] 2004	CVVHF	> 150 ml/min	4.3 mmol/L (iCa post-filter < 0.3 mmol/L)	aPTT 60–80 s	70 vs 40 (*p* 0.0007)	46 vs 74% (ND)	Major bleeding 0 vs 4.3% (ND)	63 vs 38% patients (*p* 0.03)	3.8 vs 0% (ND)	3.8 vs 0% (ND)
Kutsogiannis et al. [13] 2005	CVVHDF	125 ml/min	3.33 mmol/L (iCa post-filter 0.25–0.35 mmol/L)	aPTT 45–65 s	124.5 vs 38.3 ($p < 0.001$)	16.7 vs 53.5% (*p* 0.002)	Definite 0 vs 9.5% Occult 2.7 vs 2.3% (*p* 0.06)	15 vs 20 units in each group (*p* 0.13)	8.3 vs 0% (ND)	None
Betjes et al. [14] 2007	CVVHF	150 ml/min	iCa post-filter 0.2–0.3 mmol/L	aPTT 50–70 s	36 vs 38.4 (NS)	56 vs 43% (NS)	0 vs 37% ($p < 0.01$)	0.43 vs 0.88 units/day (*p* 0.01)	0 vs 7.4% (ND)	9.5 vs 0% (ND)
Stucker et al. [16] 2015	CVVHDF	100–200 ml/min	3 mmol/L (iCa post-filter 0.25–0.3 mmol/L)	UFH ≥ 500 IU/h	49 vs 28 (*p* 0.004)	3 vs 18% (ND)	Total 0 vs 4% (ND)	No data	3 vs 0% (ND)	6 vs 1% (ND)
Zarbock et al. [19] 2020	CVVHD CVVHDF CVVH	100–120 ml/min	iCa post-filter 0.25–0.35 mmol/L	aPTT 45–60 s	44.9 vs 33.3 ($p < 0.001$)	31.6 vs 56.7% ($p < 0.001$)	5.1 vs 16.9% ($p < 0.001$)	67.2 vs 63.4% patients (*p* 0.34)	2.4 vs 0.3% (ND)	1.4 vs 0.3% (ND)

iCa ionized calcium, *UFH* unfractionated heparin, *aPTT* activated partial thromboplastin time, *ND* no data, and *NS* no significance

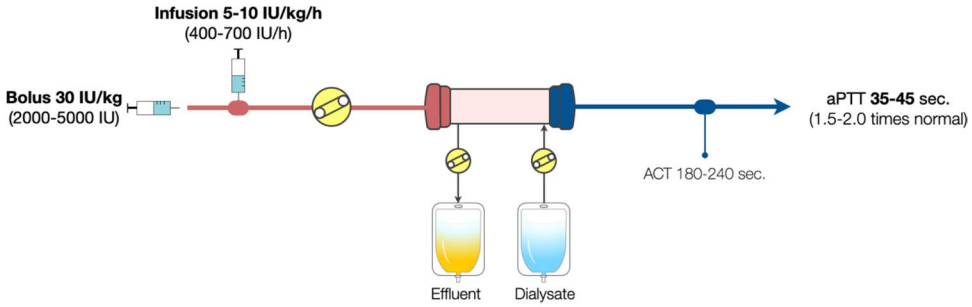

Fig. 1 Heparin resistance in critical ill patients. UFH is generally administered as a bolus of 2000–5000 IU (30 IU/kg), followed by a continuous infusion of 400–700 IU/h (5–10 IU/kg/hour) into the arterial limb of the RRT circuit. aPTT is maintained between 34–45 s or an aPTT of 1.5–2.0 times normal

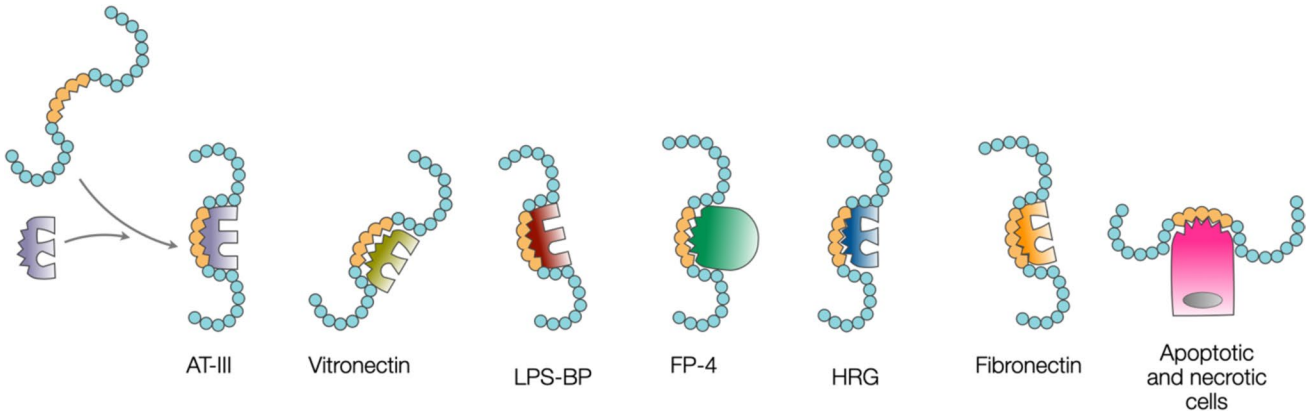

Fig. 2 Heparin resistance in critical ill patients. Heparin-binding proteins, including acute-phase reactants like platelet factor-4 (FP-4), histidine-rich glycoprotein (HRD), vitronectin, fibronectin, and lipopolysaccharide-binding protein (LPS-BP), are released from endothelial stores in critically ill patients, and their levels increase in sepsis and other forms of inflammation. Heparin has a strong affinity for apoptotic and necrotic cells, specifically to discrete domains released from the nucleus onto the membrane as the cell dies. The heparin-binding sites on apoptotic cells also signal phagocytic clearance, and thus, heparin may delay such clearance. The affinity of dead cells decreases with heparins of lower molecular weight

decrease in circulating levels of antithrombin III, both due to decreased synthesis and increased hepatic clearance, and to receptor antagonism by elastase of neutrophils [26].

At higher anticoagulation levels, filter survival increases; however, hemorrhagic events increase proportionally, being the most frequent those associated with vascular accesses and respiratory mucosa [27]. Heparin-induced thrombocytopenia is a rare complication (it is described an 3–5% incidence in cardiac surgery studies), but potentially serious. It occurs 5 to 14 days after the start of the drug and can cause venous and/or arterial thrombotic events. Its diagnosis can be difficult in critical ill patients given the high prevalence of thrombocytopenia secondary to various causes, requiring early suspicion to discontinue its use and initiate an alternative anticoagulant at a therapeutic dose to avoid massive thrombin generation and serious complications [28, 29].

The binding of heparin to AT has been shown to potentiate its anticoagulant effects. However, this interaction may also inhibit the anti-inflammatory actions of AT (Fig. 3). These anti-inflammatory effects of AT are mediated by its binding to glycosaminoglycans on endothelial membranes, leading to enhanced formation of prostacyclin [30]. In patients with sepsis or undergoing ischemia reperfusion, the levels of elastase are known to increase. Recent studies suggest that heparin, which normally potentiates AT, may inactivate AT in the presence of elastase. This process can lead to proinflammatory and procoagulant effects on the endothelium in sepsis, which can compromise the microcirculation and threaten tissue perfusion [31].

Another systemic effects of heparin that are described in the literature are hypertriglyceridemia and osteoporosis. Heparin has been shown to deplete lipoprotein lipase, reducing triglyceride clearance by liver and endothelium, leading to hypertriglyceridemia [32]. In relation to osteoporosis, its effect was studied in patients on hemodialysis, who presented elevated levels of tartrate-resistant acid phosphatase, reflecting increased osteoclastic activity and risk of osteoporosis, which decreased when rotating to LMWH [33]. Experiments in rats

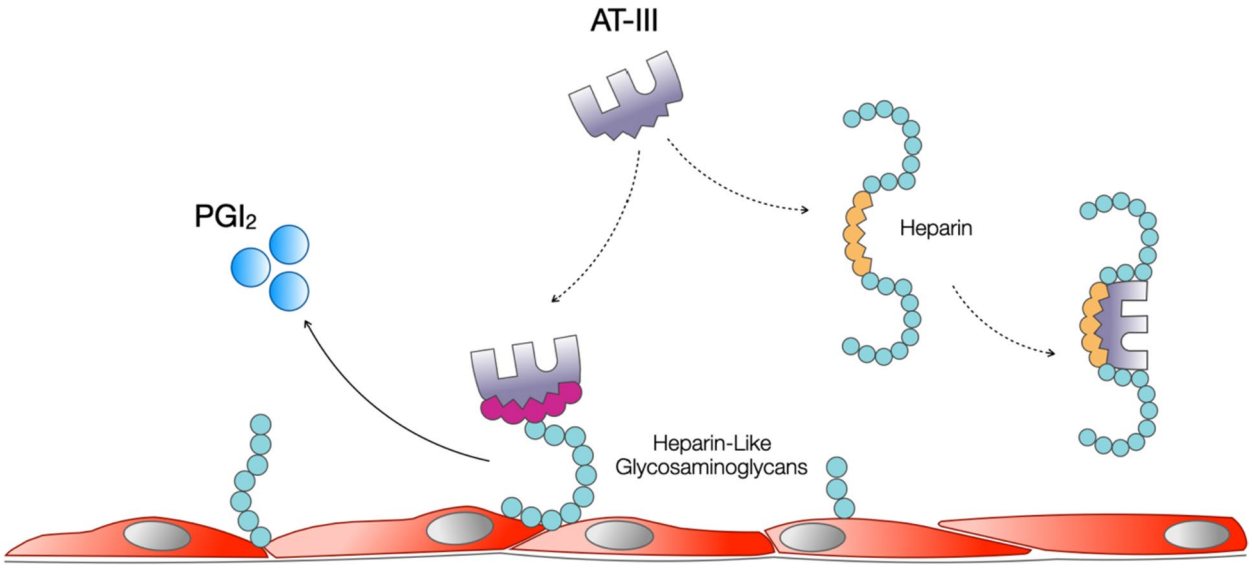

Fig. 3 Proinflammatory effects of heparin. Antithrombin III (AT-III) binding to glucosaminoglycans on endothelial membranes enhances the formation of prostacyclin (PGI2) and heparin binding to AT abolishes this effect

have shown that heparin accumulates in bone tissue, meaning that its effect is not fully reversible [34].

To avoid all systemic adverse effects of heparin, regional anticoagulation protocols with heparin have been implemented. The neutralization of heparin with protamine has been studied mainly in cardiac surgery. This is a cationic peptide that neutralizes the effect of heparin by electrostatic binding between its positively charged arginine groups with the negatively charged heparin molecule. The heparin–protamine complexes are formed in a 1:1 ratio, allowing its progressive release from antithrombin III and thus inactivating the action of heparin [35] (Fig. 4).

The dosage is based on protamine–heparin ratios, and there are studies that compare the administration of protamine in a ratio of 0.8, evidencing adverse effects (coagulopathy, bleeding, and need for transfusions) associated with higher ratios [36–38]. Protamine can cause severe anaphylactic reactions with vasoconstriction of the lung territory, secondary to the formation of IgG and IgE antibodies. Hypotension secondary to vasoplegia, thrombocytopenia, and complement activation has also been described [35]. Given this background, other protocols with fewer systemic adverse effects have been developed to generate regional anticoagulation.

Why is citrate a better option?

Citrate is a small (298 Dalton) water-soluble organic acid that is used in two forms: sodium citrate and dextrose citrate [39]. Its anticoagulant properties are secondary to its great affinity for divalent ionic calcium, forming citrate–calcium complexes in the blood, and thus decreasing the levels of ionic calcium (Fig. 5). Calcium is the most important cofactor of the enzymatic reactions of the coagulation cascade, so when its ionic form is at levels lower than 0.25–0.33 mmol/L, a significant anticoagulant effect is generated, and this is achieved with a citrate concentration of 3 to 5 mmoL per liter of blood [40, 41]. Therefore, most protocols aim to deliver this fixed concentration of citrate into the pre-filter blood line by coupling the citrate pump with the blood flow pump; thus, if less citrate is desired, it is sufficient to decrease the blood flow. Likewise, if the therapy is CVVHD or CVVHDF, increasing the dialysate will favor a greater elimination of citrate–calcium complexes. In this way, strict control of metabolic load can be maintained.

Its metabolism occurs in the liver, muscle, and kidney, entering the Krebs cycle (tricarboxylic acid cycle) (Fig. 6) and generating three molecules of sodium bicarbonate per citrate molecule and 593 cal per mmol/citrate [42, 43]. If this process occurs normally, plasma alkalinization is generated, an effect which could be beneficial for metabolic acidosis secondary to acute kidney injury. Metabolic capacity is saturable and may be reduced in situations of liver failure [44], hypoperfusion states with decreased oxygen delivery for proper functioning of the Krebs cycle, and intoxications that generate mitochondrial blockade, such as biguanides, paracetamol, and propofol [45]. The previously described situations should not be an absolute contraindication for the use of regional anticoagulation with citrate, but rather should be an indication for stricter monitoring [46]. An exception is the presence of rhabdomyolysis added to liver or kidney

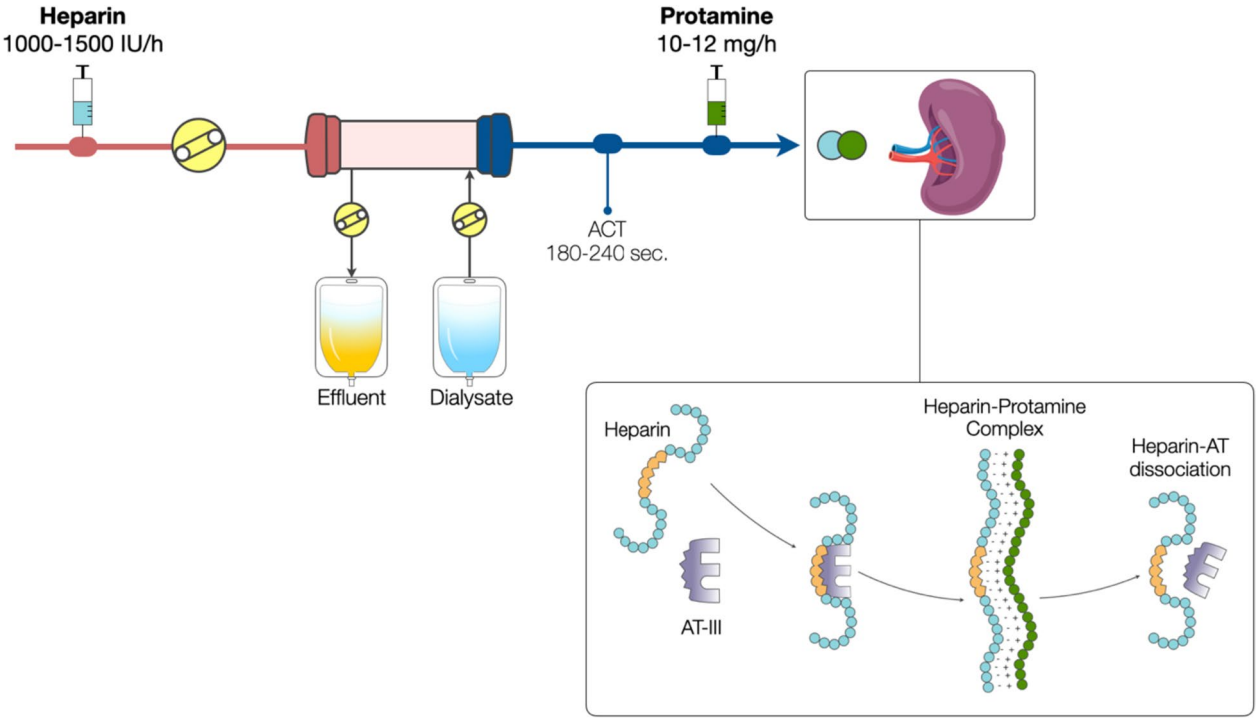

Fig. 4 Regional unfractionated heparin–protamine. Regional anticoagulation of the circuit is achieved by constant infusion of UFH into the hemofilter arterial line along with a constant infusion of protamine administered post-filter on the return line of the extracorporeal circuit. Although most protocols are difficult to standardize, in practice, UFH at 1000–1500 IU/hour is infused pre-filter and neutralized with post-filter protamine at 10–12 mg/h. The heparin–protamine complex is taken up by the reticuloendothelial system and broken down, but then heparin and protamine are released back into the circulation

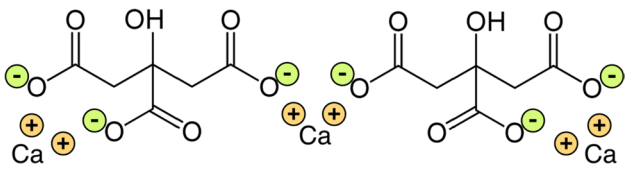

Fig. 5 Citrate–calcium complex. The separation between the two positive charges of calcium is equivalent to the separation between two citrate carboxylate radicals. One of the carboxylate radicals is not bound, resulting in a residual negative charge and a slightly acidic effect

failure, which will generate a significant decrease in muscle citrate clearance and a high risk of accumulation [47]. Since the above situations are generally associated with high lactate levels, both a high level at the start of therapy or a progressive increase could be a predictive indicator of citrate intolerance, as well as a decrease in prothrombin time [48, 49].

Regional anticoagulation with citrate was began to be used in the early 1990s. There are numerous protocols for its implementation, which have in common the administration of a pre-filter citrate solution, coupled to the rate of blood flow, in order to achieve the desired concentration of 3–5 mmol per liter of blood (Fig. 7). The use of concentrated citrate is preferred for purely diffusive therapies, combining it with dialysis solutions with lower sodium and bicarbonate concentrations to avoid adverse hydroelectrolytic and acid–base effects [50]. Diluted citrate is mainly used in convective therapies, acting as predilution replacement fluid [45].

Monitoring of regional citrate should be done with different targets. Post-filter ionic calcium measurement is used to monitor an adequate degree of circuit anticoagulation, with goals of 0.2–0.35 mmol/L [39]. In parallel, a systemic ionic calcium measurement should be performed since citrate–calcium complexes are eliminated through the dialyzer in a variable proportion depending on the technique (30–60%) and administer intravenous calcium in order to maintain normal serum levels and thus avoid adverse effects secondary to hypocalcaemia [39]. Generally, dialysis and substitution solutions do not content calcium, since this way less citrate is used, which is intended only to chelate calcium from the blood. Additionally, in diffusive therapies (CVVHD and CVVHDF), the absence of calcium in the dialysate favors diffusive clearance of citrate–calcium complexes; however, more recent research using replacement solution that contain calcium

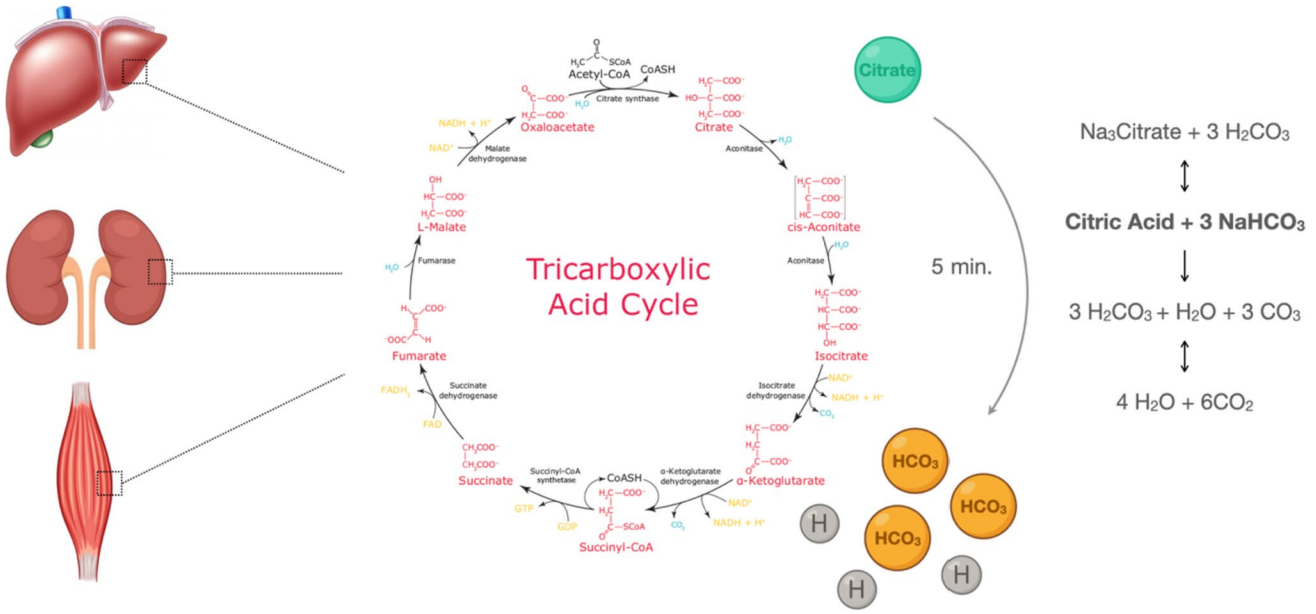

Fig. 6 Citrate load metabolism in regional citrate anticoagulation. The amount of citrate that remains in the body after being infused into the extracorporeal circuit is called the metabolic load of citrate. This load can be calculated by subtracting the amount of citrate lost in the effluent from the amount infused. The liver plays a primary role in breaking down this citrate load through the aerobic pathways of the Krebs cycle, with skeletal muscle and kidneys contributing to a lesser extent. Thus, the overall balance of citrate in the body, which determines systemic citrate levels, is determined by the difference between the citrate load and its metabolic disposal. Although patients with liver disease may experience reduced metabolic clearance of citrate and prolonged half-life, there have been no significant differences in citrate kinetics between patients with acute kidney injury and those with normal renal function. Citrate, in addition to providing regional anticoagulation by chelating calcium, also acts as a buffer. It is rapidly converted to bicarbonate. In this process, citric acid, which has a short plasma half-life of approximately 5 min, is metabolized to CO_2 and H_2O and the final net production of bicarbonate will depend on the proportions of sodium and hydrogen in the citrate solution. Bicarbonate gain from citrate loading has a positive effect in correcting AKI-related metabolic acidosis. On the other hand, excessive bicarbonate generation that overcomes base deficiency will cause metabolic alkalosis

has demonstrated a reduction in the need for intravenous calcium infusion [51, 52].

Citrate accumulation can be a potentially serious complication and can be identified by measuring citrate levels [53], which are poorly available, since plasma citrate has a very rapid metabolism and remains for approximately 5 min before being completely transformed into bicarbonate. For this reason, indirect signs should be evaluated, which have high predictive value: total calcium/ionic calcium ratio ≥ 2.5 (reflecting an increase in calcium bound to anions), a progressive increase in intravenous calcium infusion requirements, and the presence of progressive metabolic acidosis with high anion gap (Fig. 8). It requires prompt management, consisting of decreasing blood flow (in CRRT machines with blood flow and citrate coupling) or stopping the citrate infusion (severe cases) and increasing the flow of dialysis and/or replacement fluid in order to increase the extracorporeal clearance rate. It must be differentiated from net citrate overload, a benign situation secondary to excessive citrate administration or decreased extracorporeal clearance (due to insufficient dialysate/ultrafiltration flows or membrane clogging) in a patient with normal citrate metabolizing capacity, instead generating metabolic alkalosis without hypocalcaemia (Table 2) [39].

Citrate also has a high affinity for ionic magnesium, so it must be monitored at least every 12 h and supplemented to avoid complications secondary to decreased blood levels [54].

Future directions

While our review has highlighted the advantages of citrate over heparin in CRRT, it opens several potential avenues for future research. First, there is a need to further investigate the potential survival benefits of citrate, as the current literature does not provide a conclusive answer. Second, the variability in regional anticoagulation protocols with citrate requires more research to develop a standardized, universally adopted protocol. Such uniformity would greatly improve the comparability and interpretability of future clinical trials and studies. The lack of formal contraindications for citrate use in the literature further warrants an investigation to identify scenarios where citrate use may be ill-advised or

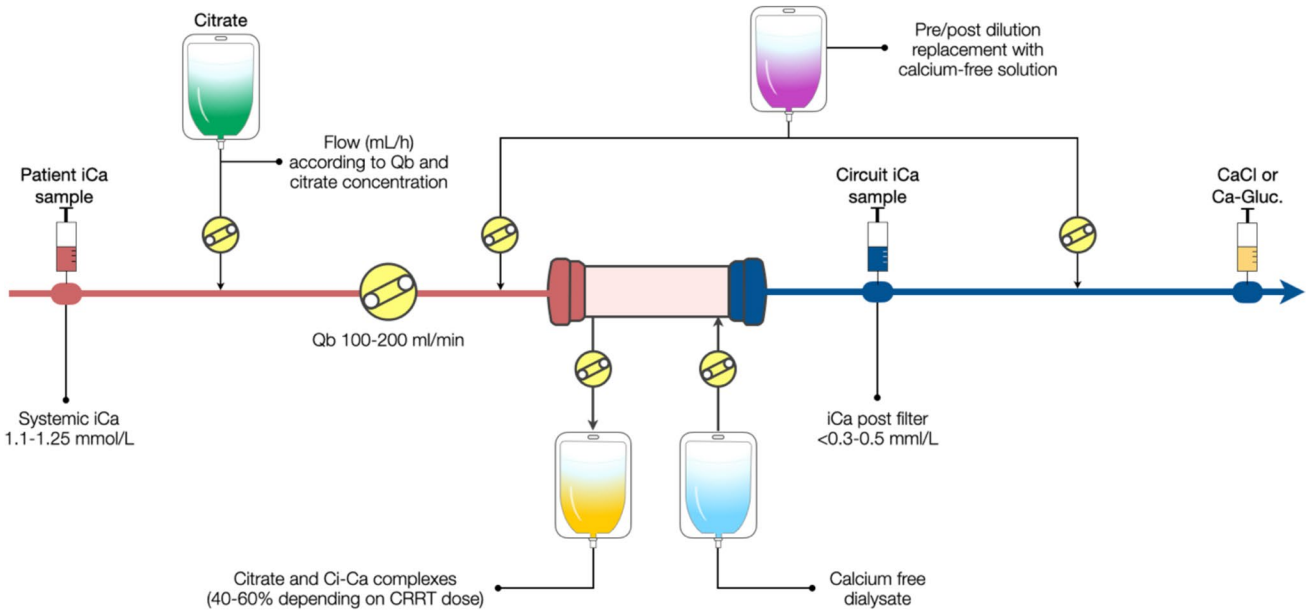

Fig. 7 Basic principles of regional citrate anticoagulation in RRT: Sampling for systemic ionized calcium is from the circuit arterial line or the patient's arterial line (to avoid the effects of vascular access recirculation). Systemic total calcium can be measured from a central venous line. *iCa* ionized calcium; *Qb* blood flow rate, *CRRT* continuous renal replacement therapy, *CaCl* calcium chloride, and *Ca-Gluc* calcium gluconate

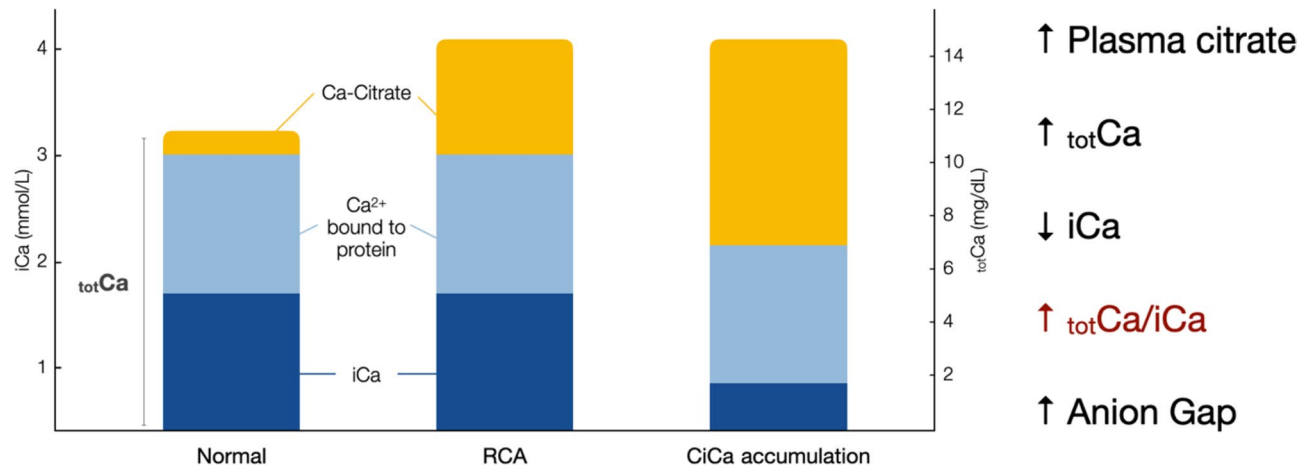

Fig. 8 Interpretation of calcium levels in citrate overload: Total calcium (totCa) is the sum of ionized calcium (iCa), the fraction of calcium bound to proteins, and calcium bound to other anions (e.g., the little amount of citrate that normally exists in plasma). During regional anticoagulation (RCA), the citrate that is not eliminated by convection or diffusion enters the bloodstream and is rapidly metabolized, although transiently, the amount of totCa may increase because more citrate will be available to bind calcium. When metabolism is decreased (severe liver and renal failure), plasma citrate will increase and bind free calcium, resulting in decreased iCa, but elevated totCa value; this is because measuring instruments that detect calcium will also measure citrate–calcium complexes in the plasma. However, the ion selective electrode that measures iCa will only measure the free fraction, which has decreased because it has been chelated by citrate. A totCa/iCa ratio ≥ 2.5 correlates well with elevated plasma citrate levels. Therefore, citrate accumulation is characterized by low iCa level (chelated by excess of citrate) and elevated totCa (citrate bound to calcium plus increased higher calcium infusion rates needed in intoxication) which result in increased totCa/iCa ratio. Also, metabolic acidosis with increased anion gap (citrate is a weak acid). Recognition or suspicion of citrate accumulation should be managed by decreasing or stopping citrate administration, but always continuing RRT to allow clearance of circulating citrate (iCa is represented in mmol/L in the figure, while totCa is in mg/dL; however, to interpret the relationship, both values must have the same measure unit)

Table 2 Metabolic disturbances associated with citrate anticoagulation

	Citrate accumulation	Net citrate overload	Insufficient citrate supply
Acid base disorder	Metabolic acidosis	Metabolic alkalosis	Metabolic acidosis
totCa/iCa	≥ 2.5	< 2.5	< 2.5
Severity	Potentially lethal	Benign, easy to resolve	Benign, easy to resolve
Frequency	Infrequent	Frequent	Infrequent
Management	Improvement by suspending citrate and increasing dialysate	Improvement by lowering the Qb (Qc) and increasing dialysate	Improvement by increasing the Qb (Qc) and decreasing the dialysate

totCa/iCa ratio total calcium and ionic calcium, *Qb* blood flow, and *Qc* citrate flow

harmful. Similarly, the establishment of an optimal regional anticoagulation monitoring strategy is yet another imperative for future research, because it is critical for ensuring safety and efficacy of the therapy. The patient population for renal replacement therapy is diverse, and understanding the specific risks associated with certain subgroups would greatly optimize the individualized management of citrate anticoagulation, enabling clinicians to better tailor treatment strategies based on patients' risk profiles. Lastly, the current literature does not provide a comprehensive analysis of the cost-effectiveness of citrate use over other strategies in CRRT. In the era of increasing healthcare costs, it is crucial to ensure that cost-effective therapies are identified and promoted to provide the best care at the least cost. Taken together, these future directions have the potential to greatly improve the use of citrate in CRRT and should be the focus of future research efforts.

Conclusion

Heparin continues to be the most widely used anticoagulant in the world given its low cost and ease of use; however, it has multiple adverse effects beyond the risk of bleeding, which can affect the outcomes of critically ill patients. The use of regional citrate makes it possible to avoid the systemic effects associated with anticoagulation. Importantly, understanding its metabolism and monitoring strategies allows for safe and well-controlled application through manual or automated protocols, effectively avoiding potentially severe metabolic adverse effects. Future research should focus on standardizing protocols, investigating survival benefits, and assessing cost-effectiveness to optimize the use of citrate and improve the care of critical ill patients undergoing renal replacement therapy. By embracing citrate's potential and refining its application, healthcare practitioners can enhance patient outcomes and deliver more targeted and safe therapies.

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Data availability The authors confirmed that the data supporting the findings of this study are available within the article.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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